REMARKS

Status of the Claims

Claims 1, 14 and 27-55 are pending in this application. Claims 38 and 39 have been canceled; new claims have not been added. Upon entry of these amendments, claims 1, 14, 27-36 and 40-55 will be pending and under active consideration.

Applicants respectfully request entry of the amendments and remarks made herein into the prosecution history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action is respectfully requested.

Support for Claim Amendments

Claims 14, 28, 40, 42, 43 and 49 have been amended. Claims 14, 28, 42 and 43 have been amended to strike recitation of "progeny" or "mixtures" of hepatic progenitors. Support for this amendment may be found throughout the originally filed specification and claims, and at least at page 8, line 17. Claim 40 has been amended to recite, in part, "hepatic progenitors [that] have the capacity to differentiate into hepatocytes or biliary cells." Support for this amendment may also be found throughout the originally filed specification and claims, and at least at page 10, lines 27-8. Claim 49 has been amended to explicitly incorporate the language of "claim 1," and accordingly finds support in the original claim.

Hence, Applicants submit that no new matter has been added by this amendment. Reconsideration and allowance of all the claims is respectfully requested.

Examiner's Response to Arguments

Applicants wish to thank the Examiner for withdrawing the prior rejection of claims 1-20 under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants further thank the Examiner for indicating that the prior rejection of claims 1-20 as being anticipated by Sargiacomo is found to be overcome in part.

Obviousness-type Double Patenting

Claims 1, 14 and 27-55 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims co-pending in USP Application Nos. 10/358,325 and/or 10/135,700. The Examiner has asserted that although the conflicting claims are not identical, they are deemed patentably indistinct from each other for reasons expressed in the record.

Without acquiescing to the propriety of the rejection, Applicants are filing herewith Terminal Disclaimers over each of the patent applications mentioned above. Applicants note respectfully that "the filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection." M.P.E.P. §804.02(II).

In view of the Terminal Disclaimers concurrently submitted herewith over each of U.S. Patent Application Nos. 10/358,325 and/or 10/135,700, Applicants respectfully submit that the obviousness-type double patenting rejections have been overcome and withdrawal thereof is respectfully requested.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Enablement

Claims 1, 14 and 27-55 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to enable one of ordinary skill in the art to make and/or use the invention for reasons of record. In brief, the Office Action states that "for example, the breadth of claim 1, which recites the expression of ICAM and lack of expression of MHC class Ia fails to be sufficient to enable isolated bipotent hepatic progenitor cells, because other cells (which are not bipotent hepatic progenitor cells) could be identified by these two markers." In support, the Examiner notes that "the specification teaches that in rat liver, MHC class I negative cells include hepatic bipotent progenitors, enucleated mature erythrocytes, and an unidentified cell population. See p. 10, lines 19-21." As well, the Office Action alleges that MHC has three alleles, "which are expressed throughout the population, and thus, the lack of expression of MHC class Ia may not, in itself, be sufficient to uniquely identify the claimed hepatic progenitors." Applicants respectfully traverse this rejection on the following grounds.

Applicants respectfully maintain that selection of cells based on expression of at least one ICAM antigen *and* lack of MHC class Ia antigen expression is indeed sufficient to isolate bipotent hepatic progenitors. In fact, the present inventors were first to fortuitously discover that the selection of cells based on lack of MHC class Ia antigen is sufficient to isolate broad classes of progenitor cells while the further selection for these MHC class Ia negative cells for ICAM expression isolates those progenitor cells of the parenchemal (*i.e.*, hepatic) lineage. This methodology is explicitly disclosed at least on page 10, lines 10-13 and the flow-chart under Example 6.11. Thus, Applicants respectfully submit that the lack of MHC class Ia expression *coupled with* positive ICAM expression (absent any further selection criteria) is sufficient to uniquely identify bipotent hepatic progenitors.

The Office Action mentions that the specification at page 10, lines 19-21 teaches that in rat liver, MHC class I negative cells include hepatic bipotent progenitors, enucleated mature erythrocytes, and an unidentified cell population. Thus, it is argued, the lack of expression of MHC class Ia may be insufficient to uniquely identify the claimed hepatic progenitors. To be sure, MHC class I negative cells *alone* do comprise this group of cells. However, the claimed invention is not to cells that are merely MHC class Ia negative. Rather, the claimed invention is directed to hepatic progenitors that are MHC class Ia negative *and* ICAM positive. In other words, the excerpt noted from the specification does *not* teach that MHC class Ia negativity is *sufficient* to uniquely identify the bipotent hepatic progenitors, but merely states that the absence of same marker is but one characteristic of hepatic progenitors. Thus, the three alleles of MHC notwithstanding, Applicants respectfully submit that the specific lack of MHC class Ia expression *coupled with* positive ICAM expression is sufficient to uniquely identify bipotent hepatic progenitors.

Thus, for at least these reasons, Applicants submit respectfully that the claims, as amended, meet the enablement requirement. Applicants solicit respectfully that the 35 U.S.C. § 112, first paragraph, rejection of the pending claims be withdrawn.

Written description

Claims 1, 14 and 27-55 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to describe the claimed subject matter in such a way as to reasonably convey to one of ordinary skill in the art that the inventors had possession of the claimed invention at the

time the application was filed. In short, the Office Action states that "although the specification provides specific guidance with regard to the isolation of single cell bipotent progenitors, the claims, as written, fail to describe these cells, because the characteristics, fail to uniquely identify this cell population. There is no specific description of a cell with expression of ICAM and lack of MHC class Ia as a bipotent hepatic progenitor cell... ." Applicants respectfully traverse this rejection.

Applicants respectfully submit that adequate written description of the claimed invention can be found throughout the specification and, at least, at Example 6.4 and Example 6.6. Example 6.4 provides identification of hepatic progenitors from fetal liver using surface antigenic markers. Specifically, Example 6.4 shows that hepatic cell suspensions stained with anti-RTIA[1]—specific for MHC class Ia—and anti-ICAM-1 could be sorted into discrete single-cell populations identifiable according to their respective staining pattern. See Figure 4. These discrete single-cell populations were then screened for clonal growth potential. The data (Table 1, Figure 4B-2, *i.e.*, gate 2) demonstrate that the $RTIA^{1-}$ and $ICAM\text{-}1^{+}$ cells yielded the greatest number of hepatic colonies, specifically "P-type colony" formation at 75.6%. P-type colonies are "clusters" of cells that divide and remain in mutual proximity and are distinctly indicative of hepatic progenitor expansion. See page 13, 3rd paragraph. These cells were also alpha-fetoprotein positive and albumin positive, further confirming their "progenitor" status. Page 21, lines 27-29.

Example 6.6 provides evidence for the *bi*potentiality of the hepatic progenitors (*i.e.*, $RTIA^{1-}$ $OX18^{dull}$ $ICAM\text{-}1^{+}$ cells)[1] mentioned in Example 6.4. Indeed, EGF is disclosed in this invention to influence both growth of the progenitor colonies and their fates as either hepatocytes or biliary epithelial cells. This is best evidenced in Figure 7, which demonstrates that the hepatic progenitors are bipotential, having the capacity to differentiate towards the biliary lineage (*i.e.*, $CK19^{+}$) or hepatocytic lineage (*i.e.*, $albumin^{+}$) based on the presence or absence of EGF.

Thus, Applicants respectfully submit that the instant claimed invention is more than adequately described in the specification to convey to one of ordinary skill in the art that the

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[1] OX18 is a pan-MHC class I antibody. That is, it recognizes an epitope common to all of the MHC class I alleles. The RT1A antibody, in contrast, recognizes an epitope *specific* for MHC class Ia. Thus, a $OX18^{dull}$ staining is understood to confirm the lack of MHC class Ia expression and a "dull" combined expression of the remaining MHC class I alleles.

claimed invention was in possession of the inventors. To this end, Applicants wish to evidence a later published paper,[2] accepted by the peer-reviewed journal PNAS, which substantially teaches the claimed subject matter. What is more, Applicants kindly note that the PNAS publication stands as one of the most cited publications from the inventors' laboratory[3] further substantiating that the invention was sufficiently enabled and described for one of ordinary skill in the art to practice and understand the invention from the original disclosure.

Taken together, Applicants respectfully submit that the instant claimed invention is adequately enabled and described under 35 U.S.C. § 112, first paragraph. Accordingly, Applicants hereby kindly solicit withdrawal of same rejections.

Claim Rejections under 35 U.S.C. § 102

Claims 14, 28 and 42-49 stand rejected as allegedly being anticipated by Sargiacomo *et al.* (*J. Hepat.*, 28:480-490, 1998) (hereinafter, "Sargiacomo") under 35 U.S.C. § 102(b). In particular, the Office Action states that the recitation of "progeny" of hepatic progenitors encompasses hepatocytes, or other cells that are differentiated from the original progenitor cells, reads on, for example, an isolated fetal liver as taught by Sargiacomo. Applicants traverse respectfully.

Applicants respectfully submit that one of ordinary skill in the art would appreciate the differences between "progenitors," "their progeny" and "mixtures thereof." However, solely in the interest of speeding prosecution of the instant application, Applicants have struck "their progeny and mixtures thereof" language in amended claims 14, 28, 42 and 43. Applicants maintain that this amendment should not be construed to limit the scope of the claims as it merely makes explicit that which would have been implicitly understood.

Accordingly, Applicants submit respectfully that amended claims 14, 28, 42 and 43, as pending, are not anticipated by the prior art, which does not teach or suggest each and every

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[2] Kubota H, Reid LM, "Clonogenic hepatoblasts, common precursors for hepatocytic and biliary lineages, are lacking classical major histocompatibility complex class I antigen," *Proc Natl Acad Sci U S A.* 2000 Oct. 24; 97(22):12132-7.

[3] Indeed, over 60 papers in the last two years have referenced the PNAS paper according to ISI Web of Science (citation index). Austin T and Lagasse E, "Hepatic regeneration from hematopoietic stem cells," Mech Dev 2003; 120:131-5 is an example.

element of the present claims, and that the rejection under 35 U.S.C. § 102(b) has been overcome. Hence, Applicants request respectfully that the rejection under 35 U.S.C. § 102(b) be withdrawn.

CONCLUSION

Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

AUTHORIZATION

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,

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